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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/735,959
Filing Date: December 15, 2003
Appellant(s): DRECHSEL ET AL.

John A. Sopp
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06/21/10 appealing from the Office action mailed 11/17/2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal Brief on 10/392,558.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-14, 16, 18-19, 22-31, 38-66, 68, 70 and 72-95.

Appellants version of the rejected claims is incorrect. Claims 20 and 71 have been cancelled.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office

action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

Claims Appendix lacks claim identifiers, except for claim 38, which incorrectly identifies (currently amended). Claim 38 contains no amendments after final.

(8) Evidence Relied Upon

| | | |
|-------------|--------|---------|
| 20010008632 | Freund | 08-2001 |
| 6491897 | Freund | 12-2002 |
| WO 9114468 | Weston | 10-1991 |
| 11/068134 | | |
| 10/392558 | | |
| 12/201149 | | |
| 11/006940 | | |

Data on decomposition of tiotropium bromide at different pH values submitted with Reply filed November 3, 2005.

Experimental findings on spray quality of formulations, submitted with reply filed April 21 2008.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14, 16, 18-19, 22-31, 50, 53-66, 68, 70, 72-80 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al (DE 19653969 as evidenced by US 2001/0008632) in view of Freund et al (WO9701329 as evidenced by US 6,491,897).

Freund et al '632 teach pharmaceutical preparations in the form of **aqueous solutions** for the production of propellant-free aerosols for inhalation for the therapy of obstructive lung diseases. Pharmaceuticals intended for inhalation are dissolved in an aqueous or ethanolic solution or a **solvent mixture of ethanol and water**. The amount of dissolved pharmaceutical in the preparation is **between 0.001 and 30%**, and preferably between 0.05 and 3%. All substances which are suitable for application by inhalation and which are soluble in the specified solvent can be used as pharmaceuticals in the new preparation. Of especial interest are betamimetics, anticholinergics, antiallergic, antihistamines and steroids, as well as combinations of these active ingredients (sections [0001] to [0007]).

Freund et al '632 teaches that addition of an effective amount of a complexing agent, such as, **EDTA, citric acid, ascorbic acid and their salts**, and more especially disodium salt of ethylenediaminetetraacetic acid, eradicates the problem of spray anomalies. The effective quantity of complexing agent Na-EDTA is between 10 and 100 mg/100 ml. Also if necessary, ethanol can be added to increase solubility up to 70% by volume. Other adjuvants such as preservatives, especially benzalkonium chloride can be added in amounts of between 8 and 12 mg/100 ml (sections [0009] to [0013]).

Freund et al '632 discloses a list of compounds which can be used as active ingredients, singly or in combination, in the aqueous pharmaceutical preparation. In individual cases, it may be required to add a higher quantity of ethanol or a solution mediator to improve solubility. The list includes; tiotropium bromide, budesonide, beclomethasone, disodium cromoglycate, etc. The solutions are set to a pH of 3.2 to 3.4

with 0.1 or 1 N HCL in 100 ml of finished preparation (see sections [0014] to [0046] and [0055]). Freund et al '632 does not specifically disclose pH levels of 2.0 to 3.0.

Freund et al '897 teach a stable ethanolic solution of budesonide suitable for nebulization (see abstract). The formulation may further comprise other active agents such as tiotropium bromide (col. 2, lines 6-49). The formulation preferably has a pH of from 2 to 7, adjusted by the amount of an acid such as hydrochloride acid (see col. 2, lines 60-67). In a preferred embodiment, the formulations comprise a quantity of a complexing agent, preferably EDTA, from about 0.1 to about 3 mg/100 mL (col. 3, lines 1-15)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations of Freund et al '632 comprising tiotropium, solvent, an acid, EDTA and other additives such as benzalkonium chloride by implementing the teachings of Freund et al '897 on lower amount of EDTA and lower pH levels, with a reasonable expectation of successfully preparing safe and stable formulations. In another word, the claims would have been obvious because the technique for improving a particular product was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. In this situation the improvement is lowering pH levels. One of ordinary skill is well aware that by adjusting the concentration of the acid the pH levels would be adjusted. Freund et al '632 teach that low pH levels are suitable for the said formulations, and one could further lower the pH levels to test for stability.

Claims 38-49, 51-52, 81-92, 94 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al in view of Freund et al and further in view of Weston et al (WO 9114468).

Freund et al and Freund et al discussed above, lack specific teachings on the inhalation device. However this deficiency is cured by Weston et al.

Weston et al discloses a metered dose inhaler which incorporates metering means for metering a quantity of fluid, and the atomizing means is provided by a mechanical break up device through which the metered quantity of fluid is passed to atomise it when it is subject to said increase in pressure (page 7, lines 5-9). For dispensing a spray of an aqueous solution of a medicament for inhalation into lungs, the droplet size is desirably less than 10 micrometers, typically 2 to 6 micrometers.

Weston also discloses that very high pressures can be generated in the pump cylinder or pressure and nozzle orifice diameters can be used, for example up to 100 micrometers, typically greater than 30 to 50 micrometers. The preferred pressures are from 50 to 400 bar, and more preferably from 100 to 350 bar with nozzle orifice of from 1 to 12 micrometers (page 12, lines 1-32).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have utilized the preparation of Freund et al., by incorporating it

in a device suitable for delivering such preparations and because it is made simpler in design and cheaper to produce and suited to its function, as taught by Weston et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1-14, 16, 18-19, 22-31, 38-66, 68, 70 and 72-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/392,558 (US 20040019073). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The

claims of the co-pending application are drawn to a formulation comprising a tiotropium salt in a concentration range of between 0.01 and 0.06 g per 100 ml of formulation, a solvent such as water and a preservative, wherein the formulation has a pH of from 2.7 to 3.1. The claims of instant application are drawn to a similar preparation. The difference is that the concentration range of tiotropium is slightly different.

This is a provisional obviousness-type double patenting rejection.

Claims **1-6, 38, 53-58 and 81** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 12/201,149 (US 20090088408). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a first active agent comprising a tiotropium salt, a steroid, a betamimetic and acceptable excipients and carrier. The claims of instant application are drawn to a similar preparation. The difference is that the steroid and the betamimetic are not required. The instant claims also require EDTA and water or ethanol/water as the solvent. However the claims of the reference employ the open language of "comprising" which allows for the other components to be included.

This is a provisional obviousness-type double patenting rejection.

Claims 1-14, 16, 18-19, 22-31, 38-66, 68, 70 and 72-95 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/006,940 (US 20050148562). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. Instant claims are drawn to formulations comprising an anticholinergic, preferably tiotropium and a second active agent such as a steroid. Formulations can be in a solution form and thus require a solvent. The preferred pH rang is from 2 to 7 (see e.g. claims 114 and 229). The claims of instant application are drawn to a similar preparation. The difference is that the second active agent such as steroid is not required.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Appellant's arguments filed 06/21/10 have been fully considered but they are not persuasive.

Appellant argues that "Freund '632 fails to disclose compositions which contain an acid for adjusting the pH to from 2.5 to 3.0" (see Brief, page 5, lines 6-7). This is not persuasive because Freund '632 teach addition of HCL to adjust the pH of the formulation. Freund prefers a pH range of 3.2 to 3.4 (see [0055] and example [0050]. Freund '897 was relied upon for teaching a pH level of from 2.0 to 7.0 and preferably from 3.0 to 4.0 (see col. 2, lines 65-67). Both documents teach adjusting the pH of the formulations by an acid such as HCL. One of ordinary skill in the art is well aware of

adjusting the pH of a formulation to optimize stability. Appellants argue that the specific pH of 2.5 to 3.0 is not disclosed by Freund '632, but show no criticality of such a pH level (see below with regard to the unexpected results) and show no inventive step in achieving the different pH. Freund '897 teach a broader range of 2.0 to 7.0 and a preferred level of 3.0 which meets the claimed pH level.

Appellant also argues that "Freund '632 does not disclose general conditions encompassing the claimed compositions since one of ordinary skill in the art would have to modify Freund '632 outside its disclosed pH range to arrive at the claimed invention".

This is not persuasive because Freund teaches the formulations can have pH of from 3.2 to 3.4. It is considered that a pH of 3.2 is not patentably distinguished from a pH of 3.0 absent any criticality. In another words, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

Appellant then argues that "Freund '632 fails to specifically direct one of ordinary skill in the art to compositions which contain sodium edentate in an amount of from 0 to 25 mg/100 ml of the composition (see Brief, page 5, lines 8-10). This argument is not persuasive either because Freund '632 teach that any amount of EDTA in the range of 10 to 1000 mg/100ml and preferably from 25 to 100 mg/100ml is suitable for the said compositions. While the preferred level of 25 mg/100ml taught by Freund '632, meets the claimed limitation, Freund '897 was also relied upon for its teachings of lower EDTA levels such as 0.1 to 3 mg/100ml. Thus Freund '632 and Freund '897 provide sufficient

teachings to one of ordinary skill in the art to prepare a formulation comprising either 25 mg/ml of EDTA or less with a reasonable expectation of preparing a suitable and stable formulation.

Appellant argues that the previously submitted evidence of the unexpected advantage and nonobviousness, demonstrates the nexus between the combination of lower EDTA-content with lower pH and the advantageous absence of spray anomalies. Appellant asserts that Table 1 of Freund '632 relates to ipratropium bromide solutions at 3.4 pH and not tiotropium salt solutions at claimed pH range. This is not persuasive because tiotropium and ipratropium are closely related compounds (both are anticholinergics) and one would expect them to behave the same under the same conditions or at least not the opposite.

Appellant argues that "one of ordinary skill in the art observing the trend in Table 1 of Freund '632 could not have expected from the reference that a tiotropium bromide solution at pH 2.5 to 3.0 and a lower EDTA amount would lead to less occurrence of spray anomalies. It is worth mentioning here that Freund '632 and a related Patent (having the same assignee as the instant application), US Patent No. 7,470,422, recite that formulations containing higher EDTA levels had no or less spray anomalies. It is also disclosed that formulations containing tiotropium or ipratropium also contained 50 mg/100 ml of EDTA (assuming with improved spray anomaly results).

The data does not show criticality or unexpected results because one can not make any conclusion about the effect of low pH and low EDTA levels on spray anomalies. At pH levels of from 2.7 to 3.0, the number of sprays at 0-50mg/100g

NaEDTA are not consistent with any conclusion. For example, at pH of 2.7 and 2.8, the formulations comprising 10 mg of NaEDTA showed 0 number of sprays with deviation, but at pH of 3.0, the formulations comprising 25mg showed 0 number of sprays with deviation. The results for the pH level of 2.7 (at 10 and 25mg) were very similar to those with a pH of 3.2, which is outside of Appellant's optimum pH level. On the other hand the number of sprays with deviation for the formulations at pH level of 2.8 and 25mg were the same as those for the pH of 3.1 and 50 mg and pH of 3.2 and 50 mg. In fact a formulation with a pH of 3.2 at 25 mg EDTA has a lower spray deviation levels (2.5%) than the formulation with pH of 2.8 and 25 mg EDTA (5.0%). Thus Appellants assertion that "An improvement of spray quality at lower pH values (2.7-3.0) in combination with lower NaEDTA concentrations (10 and 25 mg) is observed" is not found persuasive.

Appellant argues that "At each given pH value where a range of Na-EDTA content is tested, the number of actuations having deviations is always less for the embodiments within the claimed scope (i.e. at 10 or 25 mg/100 ml Na-EDTA) compared to embodiments at 50 mg/100 ml Na-EDTA. While the statement may be correct, this is not sufficient to support criticality of the levels. The criticality of a specific range is shown compared to the ranges outside of the claimed ranges. Here, the 0 and low levels of anomalies are observed with pH levels outside of the claimed levels and amounts outside of the claimed Na-EDTA amounts. For example, at pH levels of 3.2 and 50 mg/100ml Na-EDTA (both of which are outside of the claimed range), the percent of anomalies is the same as that for pH of 2.8 and 25 mg/100 ml (both show anomaly of 5%). Furthermore, it is noted that Appellant's statement is also true for the

pH ranges outside of the claimed range. At pH levels of 3.1 and 3.2 the percent anomaly increases as the amount of Na-EDTA increases. For pH level of 2.8 there are no data at 50mg and at 0 amount of Na-EDTA, there are no anomalies for 2.7 and 3.3. Equally data is inconclusive for other ranges. For example, an amount of 25 mg of Na-EDTA produces 2.6% anomaly at pH of 2.7, 5.0% at pH of 2.8, 0% at pH of 3.0 and 2.5% at pHs of 3.1 and 3.2. Thus Examiner is unable to make any conclusions from the data based on Appellant's assertion of unexpected results for the specific pH range of 2.5 to 3.0.

Additionally, not only the submitted data does not support Appellant's assertion of unexpected results for the claimed range, there is no side-by-side data comparing the instant claims to that of the closest prior art.

Appellant argues that for the same reasons as above rejection of claims over Freund et al and Freund et al in view of Weston et al should be withdrawn. This is not persuasive because as mentioned above, one of ordinary skill in the art would have been motivated to employ a suitable device for the administration of an inhalation formulation. Weston et al teach a suitable device and disclose its advantages.

With regard to the rejection of claims over co-pending applications Appellants state that the said co-pending applications qualify as "later-filed" application and that the provisional rejections should be reversed. This is not persuasive and while the instant application is under rejections the said provisional rejections will be maintained.

Rejections under provisional Double Patenting are maintained until such time as allowance.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Mina Haghighatian/

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